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(54) Title: GASEOUS ULTRASOUND CONTRAST AGENTS

(57) Abstract

This invention relates to methods for ultrasound imaging utilizing a gas or mixture of gases capable of forming bubbles after administration.

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GASEOUS ULTRASOUND CONTRAST AGENTS

The present invention relates to compositions useful for ultrasound imaging and to the use of such compositions.

Since the early days of the use of ultrasound for in vivo diagnostic imaging, there has been an ongoing interest and effort to discover and develop agents suitable for providing contrast to the ultrasound images. Generally, gases have been found to provide the best contrast for intravascular images. The earliest success may have been the work of Gramiak et al., Radiology 92, 939-948 (1969), wherein they demonstrated enhanced echogenicity following the rapid intravascular injection of various solutions in humans. Of those tested, the most echogenic was the dye indocyanine green which was observed to have present in the bottle a minute amount of foam to which the contrast effect was attributed. Since then, many accounts of echogenic contrast have been reported for right heart studies, e.g. shunt detection, after i.v. injection of agitated solutions, including blood, saline, X-ray contrast agent and the like, the agitation forming visible and smaller bubbles within the solutions. However, such agents injected intravenously are restricted to right heart imaging since the bubbles produced are too large to pass the

capillary bed of the lungs wh re the bubbles are trapped and easily broken. The use of such bubbles on th left side f the heart has b en limit d sinc the requirement of placing an arterial catheter is generally inconsistent with the noninvasive nature of the ultrasound examination. To provide for gas bubbles which can traverse the capillary bed of the lungs and provide for ultrasound echogenicity of the arterial circulation and organs subserved by the arterial circulation, most attempts have featured efforts to entrap or encapsulate gases within small size-controlled microspheres or particles composed, for example, of albumin, gelatin, sugars and the like. Such encapsulated gases may then be protected from trapping and breakage during passage through the pulmonary circulation. Although a number of early attempts were made to provide for this performance property, it was not until the mid-1980's that such agents were discovered as described in Feinstein U.S. 4,718,433.

Although these early attempts provide for contrast of the arterial circulation, they hav certain disadvantages in their use. Such disadvantages include the need for some agents to b infused continuously or injected frequently in order to provide ongoing contrast because of the lability of these bubbles to the pressures encountered in the

arterial circulation. In these cases, relatively high doses f the encapsulating materials may need to be administered which may affect the safety of the agents. As well, the need to administer these agents by intravenous injections carries all the attendant disadvantages of accessing the vascular space, i.e. the needle puncture and risk of bleeding, clotting, hematoma, and disease transmission (hepatitis, etc.) Finally, none of these agents have a demonstrated ability to cross the capillary endothelium and enter the nonvascular extracellular fluid space or the intracellular space, therein limiting their usefulness to blood vessel contrast and not permitting tissu perfusion data in a manner similar to the well-established nuclear medicine procedure employing thallium-201 for heart imaging studies. Hence, th current agents offer a less than optimal method t provide for arterial ultrasound contrast.

An object of the present invention is to provide ultrasound agents which would obviate or lessen the problems and disadvantages cited above.

This invention relates to ultrasound contrast agents comprising pharmaceutically acceptable gases or gas mixtures capable of forming gas bubbles after administration in the arterial and/or arteriolar circulation and the tissues supplied by said circulation of a warm blooded animal. The gas bubbles

ar f appr priate size t enhance ultrasound imaging. It was quit surprising, and contrary t teachings in physiology and pharmac l gy, that selected gases r gas mixtures after administration form gas bubbles within the arterial circulation under conditions which provide for diagnostic ultrasound contrast imaging in both 2D echo and Doppler contrast procedures. Mor importantly, these gases can be transported across the capillary and cell membranes and reform bubbles within the extracellular and intracellular space of the tissue to be imaged.

Another feature of this invention is the use of these agents to enhance the contrast of a diagnostic ultrasound procedure on a warm blooded animal. Still another feature is a sterile composition comprising the agent. Another feature is the use of said compositions to enhance the contrast of magnetic resonance imaging.

The gases and gas mixtures useful in the practice of this invention are best composed of gases which tend to form larger bubbles in the blood and tissues and might be typified by xenon and nitrous oxide and other weakly active general anesthetics such as sulfur hexafluoride. However, many other types of nontoxic gases, such as other perfluorocarbons, would be useful, provided they form bubbles in the blood of the appropriate size. Furthermore, the use of gas

mixtures under varying conditions f barometric pressure are useful and advantage us. For exampl , maximum bl od/tissue contrast might be expected in cases where the inhaled partial pressure of the gas mixture is retained at a high percentage of the inhaled gases and the barometric pressure of the environment is reduced. In this situation, the size of the bubbles should grow and provide enhanced tissue contrast. Conversely, decreased contrast might be expected with smaller bubbles and, in cases wherein the subject is imaged under hyperbaric conditions, the latter compressing the gas back into solution. It may be possible to provide an assessment of relative differences in tissue perfusion merely through the inhalation of room air and imaging first under hypobaric conditions to optimize contrast and then reimage as the barometric pressure is increased t monitor the disappearance of contrast. Although such may be possible with room air, any differences should be enhanced by the inhalation of an optimized gas mixture.

The composition of such ultrasound contrast gas mixtures may be varied, but in practice should always contain oxygen to insure proper oxygenation if the gas is to be inhaled for a significant period of time. Typically, the mixture would be of two or three gases, but might, on occasion, include more complex mixtures.

The gas mixtures would be prepared according to the art using those available from the fractionation of air (oxygen, carbon dioxide, nitrogen, xenon, argon, krypton, neon, helium, etc.) and those prepared synthetically, such as the perfluorocarbons, etc. Normally, 15-25% of oxygen is present.

Although ultrasound contrast may be achievable using room air alone or under hypobaric conditions, optimized formulations and mixtures would be composed of gases which would form bubbles of optimum size in the tissues. Typically, these would be those gases which are poorly soluble in oil and somewhat more soluble in water and which would have a low partition coefficient when exposed to olive oil, i.e., those which would be described as weak or poor anesthetic agents (See Goodman & Gilman, The Pharmacologic Basis of Therapeutics, 8th Ed., 282). Such agents for maximum efficacy should have olive oil:gas partition coefficients of less than about 5:1 at 37 degree centigrade, i.e., body temperature. Agents which would not generally be acceptable include the highly potent anesthetic methoxyflurane, and those less potent, but very effective, anesthetics such as chloroform, cyclopropane, halothane, enflurane, diethyl ether, fluoroxene and enflurane. Gases with maximum efficacy would include nitrous oxide, xenon, ethylene, sulfur hexafluoride, argon, and the like.

The basis on which the various gases might be optimized would be based on their oil:gas partition coefficients being reflected in the size of the gas bubbles which they form in the body formed within the body. Generally, the potent and clinically used anesthetics listed above form gas bubbles of 4 microns or less, most of which are less than two microns. Ultrasound is poorly reflected by such small bubbles and therefore these agents would be predicted to provide poor contrast especially at safe and/or subanesthetic concentrations. However, nitrous oxide can form gas bubbles in the body as large as 7-8 microns, a size which provides for excellent ultrasound reflectivity and those gases with similar oil:gas partition coefficients, namely, xenon and ethylene, would be expected to produce similar sized bubbles in the body (Goodman & Gilman above). As one progresses toward even lower oil:gas partition coefficients, e.g., sulfur hexafluoride and argon, the size of the bubbles should continue to increase, further enhancing the noted contrast. Although not clearly identified as to point of cut-off, it is probable that gases with very low oil:gas partition coefficients might become less effective by virtue of being too soluble in water. Nitrogen might be such a gas under most physiologic conditions and it has an oil:gas partition coefficient of about 0.1. Therein

the gases t pr vide in viv ultrasound contrast when inhal d sh uld ptimally include those with liv oil:gas partiti n coefficients between about 10:1 (high) and about 0.01:1 (low), preferably from about 5:1 (high) to 0.1:1 (low). In addition, any gas mixture which needs to be inhaled for any significant length of time in order to provide optimal contrast, would need to have oxygen as a necessary component gas, usually at about 20% by volume.

Examples of effective gas mixtures would include:

1) 20% oxygen; 80% sulfur hexafluoride

2) 20% oxygen; 20% nitrogen; 60% nitrous oxide

3) 20% oxygen; 20% nitrogen; 60%xenon

4) 20% oxygen; 20% nitrous oxide; 60% sulfur hexafluoride

5) 20% oxygen; 20% xenon; 60% sulfur hexafluoride

6) 20% oxygen; 20% ethylene; 60% sulfur hexafluoride

Clearly, a number of the many synthetic fluorocarbon gases could be substituted for or added to sulfur hexafluoride.

In the practice of this invention, the agents are used in the usual manner. The gas or gas mixtures may be sterilized prior to administration or administered through a sterile filter. For example, an organ or tissue would be imaged prior to the administration of the gas mixture(s) in order to obtain a control tissue ultrasound signal level. This would be accomplished

using one of the readily available commercially marketed ultrasound machines such as Acuson, Toshiba, Hewlett Packard, ATL and the like. Then an agent of this invention would be administered by inhalation by the use of equipment well known to the art, either from a single gas container with the gases premixed or via the use of gas mixing valves and using two or more gas containers as appropriate. The inhaled gas mixture would then circulate to the tissues via the blood stream and be distributed to each tissue in a manner consistent with the blood supply to the tissue. By monitoring the ultrasound signal build up, either with 2D echo and/or color Doppler mapping, one could compare the blood flow to various tissues over time. Clearly, such procedures would be readily repeatable following short breathe-out periods and this would allow for both control and stress test studies to be conducted during a short time frame. The control (normal) test as described above would be repeated after exercise or following the administration of pharmacologic stress agents to assess blood flow deficits or slower signal build up in low flow areas of the body. Such rest and stress protocols have been used for some time in nuclear medicine as the thallium (Tl-201) stress test.

Typically, the inhalation of gases to provide the above ultrasound contrast will be for times suitable

f r ultrasound imaging, usually short periods, generally less than about five minutes, but c uld be pr longed depending on the clinical application, .g., monitoring of the return of tissue perfusion after a period of ischemia. Conversely, one might inhale the gas mixture for a very short period of time in order to get transient type information such as first pass organ/tissue perfusion, etc. Therein it is envisioned that the gas or gas mixtures might be inhaled over broad time frames with the clinical use determining the individual administration protocol.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compositions or procedures shown or described. Obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

Claims

1. The method of ultrasound imaging of a warm blooded animal comprising administering an ultrasound contrast agent comprising a pharmaceutically acceptable gas or mixture of gases in an ultrasound diagnostic amount for a period suitable to image and thereafter ultrasound imaging said animal, said gas or mixture of gases being capable of forming bubbles after administration of a size appropriate to enhance imaging in the arterial or arteriolar circulation and tissues supplied by said blood circulation.

2. A composition for ultrasound imaging comprising a pharmaceutically acceptable gas or mixture of gases, said gas or mixture of gases being capable after administration of forming bubbles of a size appropriate to enhance imaging in the arterial or arteriolar circulation and tissues supplied by said blood circulation.

3. The composition of claim 2 wherein the ultrasound said gas is xenon.

4. The composition of claim 2 wherein said gas is ethylene.

5. The composition of claim 2 wherein said gas is nitrous oxide.

6. The composition of claim 2 wherein said gas is sulfur hexafluoride.

7. The composition of claim 2 wherein said gas is argon.

8. The composition of claim 2 wherein said gas is selected from the group consisting of a perfluorocarbon gas.

9. The composition of claim 5 wherein the agent additionally contains oxygen.

10. The composition of claim 6 which additionally contains oxygen.

11. The method of claim 1 wherein said gas is xenon or a mixture of xenon and oxygen.

12. The method of claim 1 wherein said gas is ethylene or a mixture of ethylene and oxygen.

13. The method of claim 1 wherein said gas is nitrous oxide or a mixture of nitrous oxide and oxygen.

14. The method of claim 1 wherein said gas is sulfur hexafluoride or a mixture of sulfur hexafluoride or oxygen.

15. The method of claim 1 wherein said gas is argon or a mixture of argon and oxygen.

16. The method of claim 1 wherein said gas is selected from the group consisting of perfluorocarbon gas and mixtures.

17. The method of claim 1 wherein the ultrasound contrast gas procedure is used to image cardiac perfusion at rest and following exercise.

18. The method of claim 1 wherein the ultrasound procedure utilizes the modes of 2D echo, doppler, color doppler or color mapping.

19. The method of claim 1 wherein the ultrasound procedure is used to assess the perfusion of any peripheral noncardiac organ or tissue both at rest and after exercise.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/08385

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 49/00, 33/04; 33/00, 31/015, 31/02; A61B 8/14
US CL :424/9; 424/600; 514/743; 514/759; 514/757; 128/662.01; 128/662.02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/9; 424/600; 514/743; 514/759; 514/757; 128/662.01; 128/662.02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	US, A, 5,088,499 (Unger) 18 February 1992, See column 2.	1-19
Y	US, A, 4,657,756 (Rasor et al.) 14 April 1987, See column 3.	1-19
Y	US, A, 4,681,119 (Rasor et al.) 21 July 1982, See abstract.	1-19
Y	US, A, 4,718,433 (Feinstein) 02 January 1988, See column 1 and 2.	1-19
P,Y	US, A, 5,078,146 (Sato) 07 January 1992, See abstract.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS
ultrasound, bubble, xenon, xrgon, perfluorocarbon, oxygen, ethylene, nitrous oxide, arteriolar, arterial, 2D echo, color doppler, color mapping